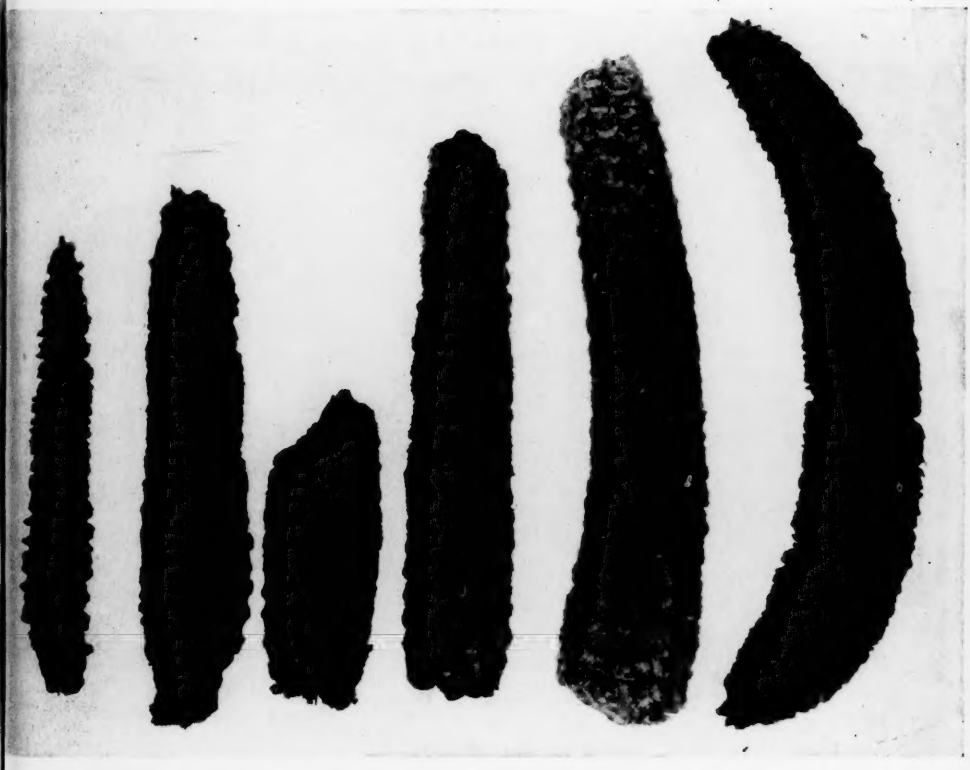
The Journal of HEREDITY



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Edward W. Lindstrom—An Appreciation

The Human "Nucleolar Chromosome"

The Greeks had Words for Six Sexes

Calculation of Inbreeding Coefficients

The Hevea Rubber Tree for Food and Oil

VOLUME 40 FEBRUARY, 1949 NUMBER 2

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THE HUMAN NUCLEOLAR CHROMOSOME

Figure 1

A—Chromosomes of spermatogonial prometaphase, Individual I (Table I and Figure 4). The nucleolus has not yet disappeared (arrow). Note four arms around nucleolus, two for each member of the pair of chromosomes. Aceto-orcein subsequent Feulgen, fast green counterstain. × 3275. *B*—Individual VI; Pachytene nucleus, showing nucleolar chromosome. Chromomeres 1-10 are below nucleolus; the other side is clear to chromomere 16. Note failure of pairing at chromomeres 3-7, and between chromomeres adjacent to the nucleolar region. Aceto-orcein, fast green. × 2500.

A CYTOLOGICAL BASIS FOR A MAP OF THE NUCLEOLAR CHROMOSOME IN MAN*

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OUR effort in the present paper is to extend the application of cytogenetic methods to problems of human heredity. The essence of the cytogenetic technique is the correlated use of genetic and cytological information, to the end that the genetic constitution of an individual may be determined more expeditiously and completely than by the restricted use of either discipline. Although human genetics is still in its beginnings, a sufficiently large number of characters has been studied to provide a linkage map for the sex chromosomes and to make further intensive analysis profitable.[8] It has not hitherto seemed likely that the establishment of correspondence between chromosome regions and their genetic effects in man would be feasible. Cytologically the most serious difficulty appeared to lie in obtaining sufficient structural detail in the chromosomes to make a useful search for differences between individuals of different constitutions.

Differences in the metaphase morphology of the various chromosomes have indeed been established; a major triumph of human cytology being Painter's analysis of the sex chromosomes.[14, 1] In view of the detail required for a cytogenetic map, however, the structure of the metaphase chromosomes has only limited uses. We have now found it possible to work out the pattern of the chromomeres of one chromosome of the complement, the nucleolar chromosome, at the pachytene stage of meiosis. These observations have extended to the production of a standard diagram for this chromosome which can serve as a basis for recognition of deviations from the normal pattern. This is at present only a first approximation. It should be possible to improve this preliminary map and to extend it to the other chromsomes of the complement. A demonstration of this material was presented at the meeting of the Genetics Society of America, at St. Louis in 1946.[16]

Material and Methods

The prime difficulty in human cytology is the scarcity of controlled material and the capriciousness with which it may be obtained. Particularly is this the case when surgical procedures are involved. We owe to Dr. Stanley P. Reimann the basic suggestion that the orchidectomies currently performed in the alleviation of prostatic carcinoma (Huggins) provide a source of material for the study of human spermatogenesis. With this material it becomes feasible to attempt a systematic study of the pachytene stage of meiosis, a stage at which chromosome analyses have been accomplished in such diverse organisms as the grasshopper, maize,[15] and *Neurospora*. To date we have had material from forty individuals. Our thanks are due to Dr. B. F. Hayllar, and recently to Dr. C. Uhle, at the Lankenau Hospital, and to Drs. Harrison and Birdsall of the Presbyterian Hospital in Philadelphia, for providing material from their practice, and for their considerate helpfulness in arranging that as short a time as possible elapse between the removal of the testes and their fixation for cytological purposes.

Most of the standard cytological techniques have already been applied to human material; even the aceto-carmine squash technique was used on human tumor tissue as long ago as 1927 by Belling,[2] the original perfector of the tech-

*Aided by a grant from Mrs. Efrem Zimbalist.
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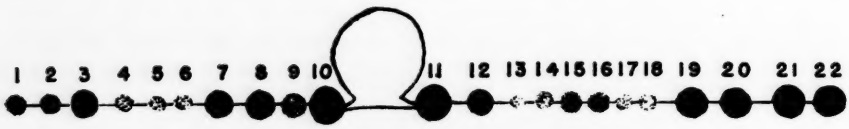
16. Note failure of pairing at chromomeres 3-7, and between chromomeres adjacent to the nucleolar region. Aceto-orcein, fast green. × 2500.



MAP OF NUCLEOLAR CHROMOSOME

Figure 2

The standard diagram of chromomere pattern for the nucleolar chromosome of man, based on the data shown in the Figures and Table. Stippled chromomeres stain lightly (contain less nucleic acid) than the heavy solid ones. Note the heavy chromomeres (10 and 11) to either side of the nucleolus (shown in outline).

nique for plant cytology. The more recent developments in the squash and smear techniques come from the work on the salivary gland chromosomes of the Diptera, particularly of Drosophilia. They consist in the breakage of the nuclei during the process of preparation, in such a way that the chromosomes lie free for individual study. At pachytene the twenty-four chromosomes of man are difficult to disentangle in the intact nucleus. The novelty in our technique that permits the analysis of the individual chromosomes consists in cutting the tubules into small fragments, from which the cells are stripped into a drop of fixative on a slide under the dissecting binocular microscope, where they can be squashed effectively under a cover slip. In this way preparations are obtained which permit the detailed analyses reported here.

Our best results have been obtained with the aceto-orcein combination of La-Cour.[13] The usual procedure is to tease the cells out of the seminiferous tubules into the fixative as soon as possible after the removal of the testes. It seems that the best stained preparations result from material so treated, and squashed after ten or fifteen minutes. The squash is made almost exactly as in the techniques familiar to Drosophila workers. The connective tissue of the tubules is removed from the preparation and a cover slip is placed upon the cells in their drop of aceto-orcein. While held firmly in place on one side by a piece of absorbent paper, the cover slip is tapped gently but thoroughly with a needle in order to break as many nuclei as possible. Excess fixative is blotted off and the preparation pressed flat by a rolling motion of the thumb.

As has already been noted by Painter,[14] and by Evans and Swezy,[7] the metaphases are relatively more sensitive to defects of fixation than are the prophases of meiosis. It was fortunate that the pachytene stages in which we were interested were both the best preserved and the most frequent in our material. There seems to be no obvious difference between the preparations derived from the two types of surgical procedure used: total castration, or the scraping out of the seminiferous tubules from the scrotum.

Other types of squash preparations have been used, and we have also made sections of some of our material, for comparison with the results of earlier investigators. For metaphase chromosomes, it has been useful to fix in an acetic-alcohol mixture, and later to stain and squash in aceto-carmine. The chromomeres at pachytene seem coarser following this treatment than they do in the aceto-orcein preparations. Occasionally the aceto-orcein or carmine preparations were marred by fatty globules, or, when the tubules were allowed to remain in the stain for some time, by crystals of the stain. In such cases the Feulgen technique has proved useful for restaining, especially with Bauer's procedure of fixing the aceto-orcein or carmine preparation in Allen's B-15 after the removal of the cover slip.

As a counter-stain in the aceto-orcein or the Feulgen procedures, fast green was used. Preparations of great brilliance are thus obtained, in which the nucleoli appear green in contrast to the

red of the chromosomal material proper.

As already noted, the best preparations are those made quickly after the operation. We have found however, that tissues stored in fixative in the frozen state, or even at temperatures around freezing, for several years yield preparations almost as good as the fresh material. This is important, inasmuch as it suggests the possibility of the storage of material by members of hospital staffs for future cytological analysis.

In this report the analysis of the nucleolar chromosome of ten individuals is presented. All except one of these was between sixty and seventy years old. As Engle has pointed out,[6] the difference between these and younger individuals is not so much in the activity of spermatogenesis as it is in the extensive increase in the toughness of the connective tissue. This has its repercussions on the ease of making preparations, among other things; the tougher the connective tissue the greater the difficulty in stripping the cells out of the tubules and obtaining a unicellular layer on the slide.

We have found no abnormality in our series of cases that could be interpreted as due to the prostatic carcinoma present in most of them. Infection, in one case, not reported in this paper, resulted in a testis with little activity; nevertheless, pachytene stages were present and could be analyzed.

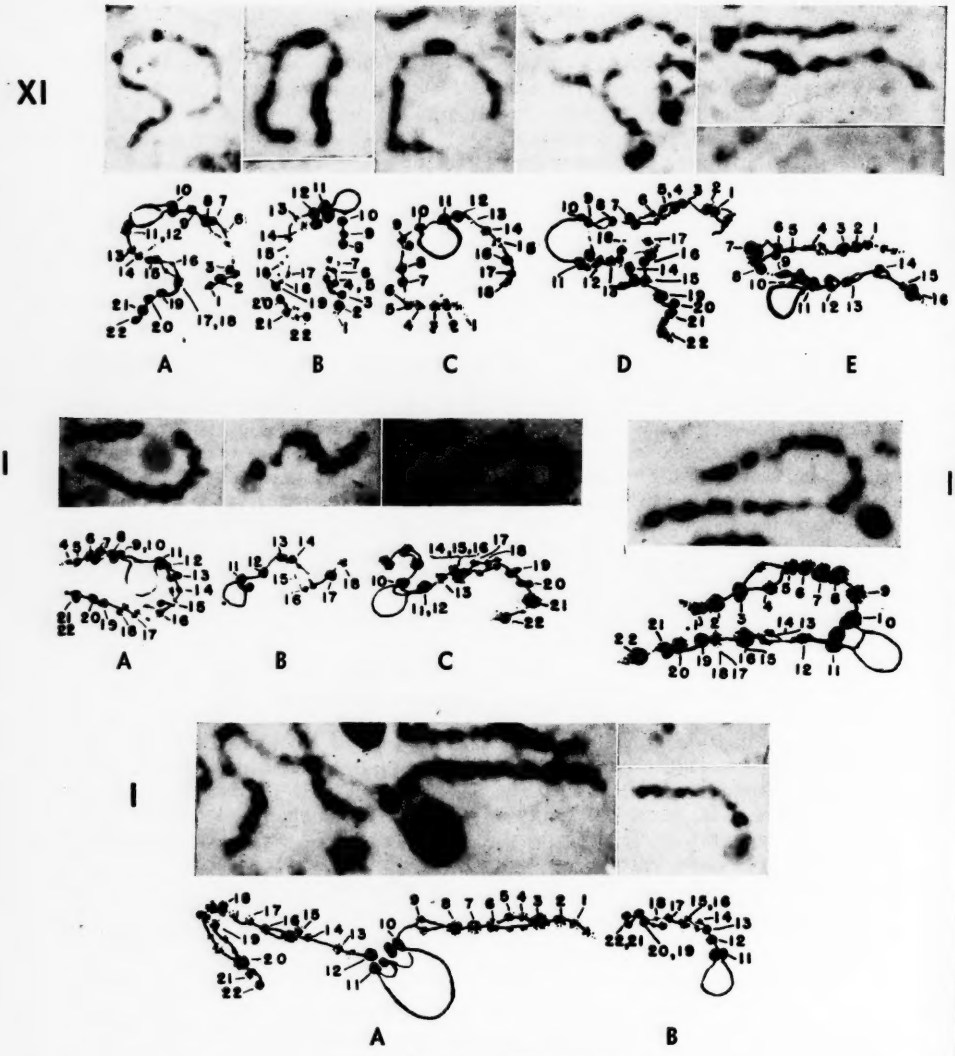
Chromomere Pattern

Our first problem was to determine the degree of constancy of chromomere pattern, both in different cells of the same individual and between different individuals. The attempt was therefore made to obtain a sufficient number of figures for individual chromosomes to permit the establishment of a standard diagram. The desirable procedure would have been the accumulation of a group of pachytene nuclei in which all chromosomes could be identified and their pattern analyzed. This proved not to be the most feasible approach. It was difficult to distinguish between artefacts produced by the squash process (breakage or adhesion of chromosomes) and possible associations of the heterochromatic regions of non-homologous chromosome pairs, without prior knowledge of the pattern which was itself the object of study. It was therefore decided to take a particular chromosome, identifiable by some striking unambiguous morphological character, and use it as the test object. The nucleolar chromosome proved useful for this purpose.

It is well known that in a variety of organisms, both plant and animal, the nucleolus is associated with a specific chromosome region. (See Kaufmann[11] for references.) Although this had not been demonstrated for mammals at the time our work was done, analysis showed that the assumption of a specific nucleolar region is correct in man also —as an examination of the figures on the various plates will show.

The preparations were searched for figures in which the nucleolus could be seen clearly and in which its associated chromosome could be traced with as little ambiguity as possible. Figures, representative of each individual, and in which the chromosomes lie as flat as necessary for photography, are shown in the plates. The camera lucida drawings below each photograph have the different chromomeres numbered in accordance with a standard diagram of the chromosome.

The construction of this standard diagram met with some difficulties, which deserve comment. While in many cases the nucleolus appeared to be medial, flanked on either side by a chromosome arm, in almost an equal number of figures the nucleolus was either terminal or sub-terminal. Two interpretations were possible: either the nucleolar chromosome was frequently broken in smearing, or there were two chromosomes concerned, whose separate nucleoli frequently fused. The former seemed the more likely possibility, but it had to be proved, since the nucleolus breaks down rather early during the prophases, leaving no constriction in the metaphase chromosomes to indicate its site of origin. One late spermatogonial prophase was found (Figure 1) in which the nucleolus per-



NUCLEOLAR CHROMOSOMES

Figure 3

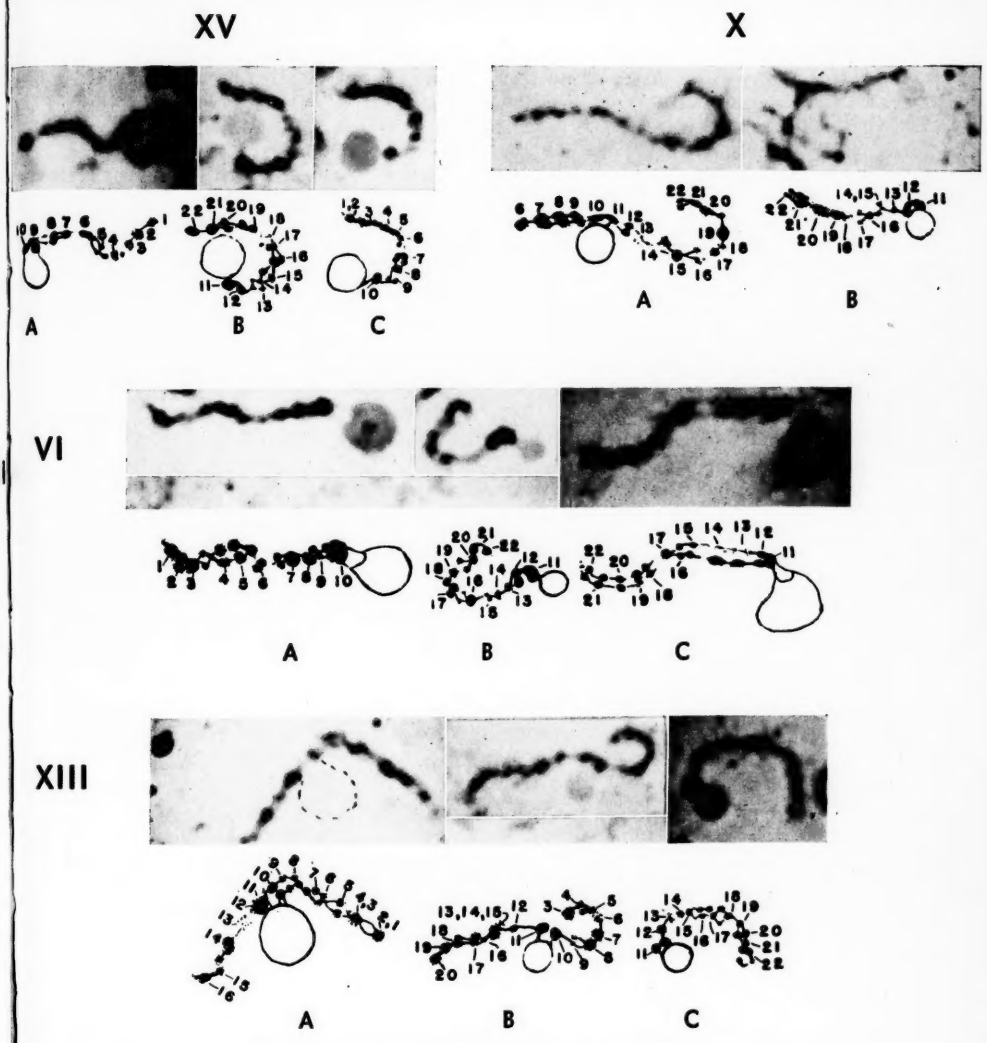
In these plates, each separate group of photographs belongs to a single individual, designated by a Roman numeral. The drawing below each photograph was made by camera lucida, and the numbers upon them are those given the chromomeres in the standard diagram (Figure 2).

Individual XI. Medial nucleolar chromosomes. Note in *D* a loop simulating the configuration typical of pairing in a heterozygous inversion. Normal pairing in other figures of this individual show this loop to be probably the result of a spiral crushed flat in smearing. In *C*, the chromosome has been broken between 18 and 19, the remainder being elsewhere in the preparation. Aceto-orcein, fast green. *A-D*, × 2200; *E*, × 3010.

Individual II. *A*—chromomeres 1-3 broken off; *B*—probably "arm #2" broken between 18 and 19; possible interpretation as "arm #1" with considerable stretching between chromomeres 8 and 10; *C*—chromomeres 1-7 broken away. Aceto-orcein, fast green. *A*, *B*, × 2200; *C*, × 2260.

Individual III. Medial nucleolus, region between chromomeres 11 and 15 stretched. Acetic-alcohol fixation, Feulgen. × 3275.

Individual I. *A*—medial nucleolus: note evidence of dual nature of nucleolus (one from each homologue) from connections with chromomeres 10 and 11, into the paired chromosomes. Acetic-alcohol fixation, aceto-carmine stain. × 2200. *B*—Broken nucleolar chromosome, chromomere 11 prominent. Aceto-orcein, subsequent Feulgen—fast green. × 2200.



NUCLEOLAR CHROMOSOMES FROM FOUR INDIVIDUALS

Figure 4

The photographs were taken using either a 90× .1.4.N.A Zeiss apochromatic objective, or a Bausch and Lomb 60× 1.4 fluorite with either a Homal III ocular, or a 12× compensating ocular. In most cases a Wratten 58B filter was used. The rest of the magnification was obtained by the position of the camera bellows.

Individual XV. Broken nucleolar chromosomes; note difference in length between *A* and *C* with chromomeres 1-10 ("arm #1"), and *B*—with chromomeres 11-22 ("arm #2"). Chromomeres 1-5 in *C* darker than usual. Aceto-orcein, fast green. × 2200.

Individual X. *A*—nucleolus faint, chromomeres 1-5 broken off. *B*—has only "arm #1". Aceto-orcein, fast green. × 2200.

Individual VI. Broken nucleolar chromosomes: "arm #1", *A*—"arm #2", *B* and *C*. In *C*, chromomeres 13 and 14 of the upper strand are pale, a peculiarity of this cell. *A* and *B*, aceto-orcein, fast green; *C*, aceto-carmine, subsequent Feulgen. × 2200.

Individual XIII. *A*—the chromomeres following 16 have been broken away; the nucleolus is very faint, and has been outlined in ink. *B*—chromomeres 1, 2, and 21, 22 cannot be seen. Aceto-orcein, fast green. *A* and *B*, × 2200; C, × 1660.

sisted, with four chromosome arms of the diploid set visible around it. The critical test would come from the identification of the centromere in the pachytene chromosomes. This has not been possible in our material, in any of the preparations by the different techniques. Fairly decisive evidence, however, came from the sizes of the nucleoli of the two types: if there were only one nucleolar chromosome, broken in the different figures, the size of the nucleolus should be fairly constant. But if two nucleolar organizers were present, which produced nucleoli that fused, there should be a difference between the sizes of the nucleoli in the cases where the two had fused, and in those where they remained separate. Since no consistent differences in size were noted, it seems most likely that we are indeed dealing with a single chromosome whose nucleolus is medially situated.

The diagram given in Figure 2 contains ten chromomeres in the left "arm," twelve in the right. It was constructed by a series of approximations from the individual figures, as being the most detailed structure likely to encompass all the variations observed. These variations were interpreted as being due to differences between cells in the degree of stretch between the individual chromomeres, to differences in the relative nucleic acid contents of the different chromomeres in a chromosome, and to differences in the over-all nucleic acid concentration of the chromosome. One test of the correctness of these assumptions comes from the ease with which the illustrated photographs can be made to fit the diagram (see Figures 3, 4 and 5). Another test comes from the classification of the chromosomes containing a nucleolus according to the chromomere pattern of the "arm." Table I contains a resumé of the data classified according to individuals. No clearly divergent figures were found; all of the nucleolar chromosomes whose pattern could be worked out could be interpreted in accordance with the standard diagram.

The cases in which the "arms" could be distinguished from each other by their chromomere pattern alone are of especial importance, in that they demonstrate the feasibility of identifying these patterns in human chromosomes. It follows that the study of the other chromosomes, not having such characteristic markers as the nucleolus should still give results, although not so easily as the nucleolar chromosome. At the same time some of the difficulties inherent in the study are brought out. The two arms may be difficult to distinguish when, for example, chromomere No. 2, in the left "arm," instead of being lighter than No. 3, has the same intensity. Since the right "arm" ends with a series of four chromomeres, which may not be well separated from each other, the ends of the two arms are sometimes distinguishable with difficulty. As can be seen by a study of the plates, the relationships between the different chromomeres are generally maintained well enough to furnish a consistent pattern.

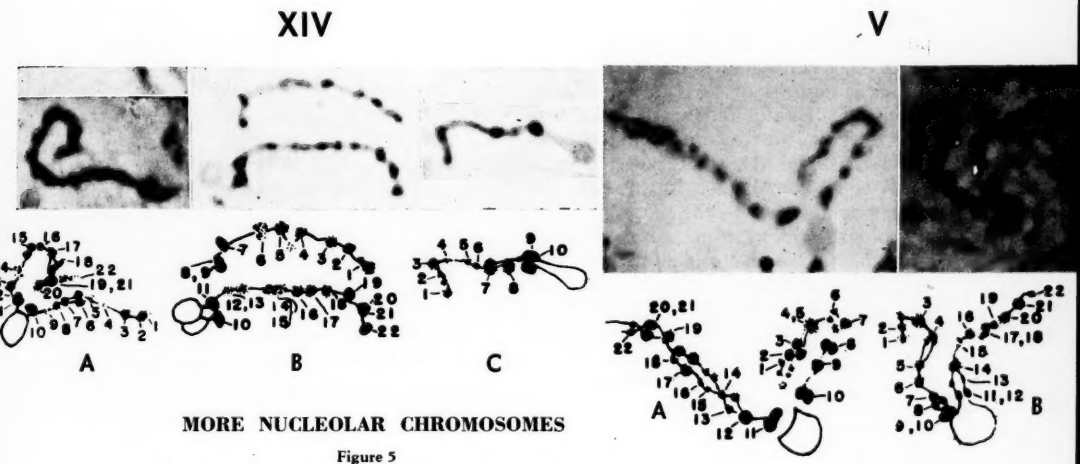
The Two Nucleolar Organizers

The presence of chromatic granules around mammalian nucleoli has been much discussed in relation to nucleolus formation.[5, 3, 4, 10, 18] The relationships of these granules to the chromosomes cannot be established without an analysis of the kind presented here. The results show that the nucleolus in man is

TABLE I. Classification of the Arms of the Pachytene Chromosome Associated with the Nucleolus, According to their Chromomere Patterns.

The chromosomes from the different individuals were classified according to the ease of their interpretation in terms of the standard diagram (Figure 2). Chromomeres 1-10 are considered to constitute "arm" no. 1, chromomeres 11-22 "arm" no. 2. The complete chromosome, with the medial nucleolus, falls in the class 1,2. Easily interpreted figures are classified as "clear"; those concerning which question could be raised are "possible." Chromosomes with a medial nucleolus sometimes had only one arm analyzable: these are listed as ?,2 and 1,?.

Individual	Pattern										
	Clear					Possible			Unanalyzable		Total
	1	2	1,2	1,?	?,2	1	2	1,2	1 or 2	1,2	
I	—	2	3	—	1	2	—	2	4	5	30
II	2	3	1	1	1	2	1	2	1	—	19
III	—	—	—	—	—	2	2	—	4	1	10
IV	3	1	—	—	—	—	—	—	3	1	9
V	—	1	1	2	—	2	1	2	4	9	36
VI	1	2	—	2	1	—	3	2	5	7	30
X	1	—	1	—	1	0	1	2	9	9	37
XI	1	—	3	1	—	—	3	1	5	11	41
XIII	1	1	1	4	—	2	2	5	1	7	40
XIV	3	—	2	2	—	3	3	2	7	3	34
XV	2	3	—	2	—	1	3	1	6	5	31
Total	14	13	12	14	4	14	19	19	49	58	317



MORE NUCLEOLAR CHROMOSOMES

Figure 5

Individual XIV. *B*—The chromosome has been broken between chromomeres 9 and 10, and both fragments are present in the figure. Fixation, 50% acetic acid with 1.25% La acetate, subsequent Feulgen stain. *A* and *C*, × 2200; *B*, × 2500.

Individual V. Nucleolus medial, between chromomeres 10 and 11. Note the looseness of synapsis, also the apparent coalescence of chromomeres 9 and 10 in *B*, of chromomeres 4 and 5 in *A*. The apparent chromomeres distal to chromomere #1 in *A* are adventitious, having nothing to do with this chromosome. Acetic-alcohol fixation, aceto-carmine stain. × 2200.

formed in association with a group of large chromomeres, essentially similar to the type of chromosome region called heterochromatic by Heitz[9] in the intermitotic nuclei[17] of plants and animals. Since the pachytene stage is comparable in meiosis to the mitotic stages with which Heitz worked, it follows that the nucleolus of man may be considered as organized under the influence of heterochromatin.

The discussion in the present paper thus far has avoided the question of the relation of the sex chromosomes to the nucleoli. The *X* chromosome is distinguishable at pachytene in our preparations, as it was in the earlier work of Painter. Our impression is that a nucleolus is formed by the X chromosome, independent of that formed by the nucleolar chromosome which we have described. The nucleolus associated with the sex chromosomes differs from that with which we have been concerned in this paper, the autosomal nucleolus (plasmosome proper), in staining less intensely with fast green, and in the pattern of its association with the chromomeres of its chromosome, the X. This analysis will be presented separately, in a communication concerned with the heterochromatic regions. It is sufficient here to emphasize that two separate nucleolar organizers are present in man.

Discussion

There are two problems to which the analysis of chromomere pattern has immediate relevance: the study of the structure of the nuclei of different tissues, and the detection of chromosome rearrangements. The relations of the nucleoli to their associated chromatic granules in such tissues as blood, nerve, and tumor may, as already stated, be defined more precisely in terms of the specific chromomere pattern. With a standard of reference supplied by the pachytene diagram, it should be possible to determine how wide a divergence exists in the nuclei of the different tissues, under both normal and pathological conditions.

The second problem having a closer bearing on human genetics is the detection of chromosome rearrangements. The technique as already developed is adequate to distinguish the presence of even small inversions. The study of in-

dividual no. XI (Figure 3) is a case in point: if the loop found in Figure 3-XI*D* had consistently occurred in all the clear figures in this individual, the conclusion would follow that he was heterozygous for a nucleolar chromosome carrying a section inverted relatively to its homologue. In this case, the loop was due, not to the pairing of two homologues one of which carried the inversion, but to an accident of preparation in this cell, since the other figures give clear evidence of a normal sequence. The discrimination between the two possibilities can be made unambiguously.

In the individuals reported here, and in the rest of our series, no inversions have been found in the nucleolar chromosome. Selection might operate in human populations to eliminate large inversions, due to the inviable gametes produced by crossing over in males carrying such inversions.[19] The single report[12] of a chromosome inversion in man seems somewhat insecurely based. The evidence comes from apparent anaphase bridges at meiosis, interpreted as resulting from crossovers between the inverted and normal chromosome, and from apparent fragments thought to be the complementary crossovers. The bridges may have been adhesions of chromosome ends. The apparent fragments may be laggard smaller autosomes. Both these phenomena are rather frequent occurrences. It is not unlikely that man will turn out to be one of the organisms in which major chromosome rearrangements are rare.

The ultimate aim of such work as the present must be to devise techniques by which rapid and detailed identification of the morphological characteristics of the chromosome complement of man can be made. As the work proceeds, the possibility may be envisaged that correspondences between the results of pedigree analysis and cytological observation will appear. This may make possible the correlation of chromomere deficiencies with genetic differences, particularly if use can be made of the increased resolution afforded by the electron microscope. It is clear that much must be done before the achievement of cytological maps in man becomes more than visionary; yet it seems equally clear that the achievement should not be impossible.

Summary

By means of an adaptation of the squash techniques for cytological analysis, it has been possible to make a study of the pachytene chromosomes of man. A standard diagram for the nucleolar chromosome is presented, based on a detailed study of ten individuals, with confirmatory data from thirty others. No inversion configurations have been found. The possible uses of the technique are briefly discussed.

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A DISCOVERY OF REMAINS OF PRIMITIVE MAIZE IN NEW MEXICO

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Botanical Museum, Harvard University

THE problem of the origin of maize which has puzzled botanists for almost four centuries is one step nearer solution as the result of the discovery made during the summer of 1948 of important prehistoric plant remains in New Mexico. These vegetal remains were uncovered by an expedition sponsored by the Peabody Museum of Harvard University* and led by Mr. Herbert W. Dick, a graduate student in anthropology at Harvard, who was assisted in the botanical aspects of the expedition by Mr. C. Earle Smith, Jr., the junior author of this paper, and an undergraduate student in biology at Harvard.

FIRST MAIZE

Figure 6

An artist's reconstruction (natural size) of the primitive pod-pop corn found in the lowest stratum of the Bat Cave refuse heap. This primitive maize shows no evidence of having been derived from teosinte.

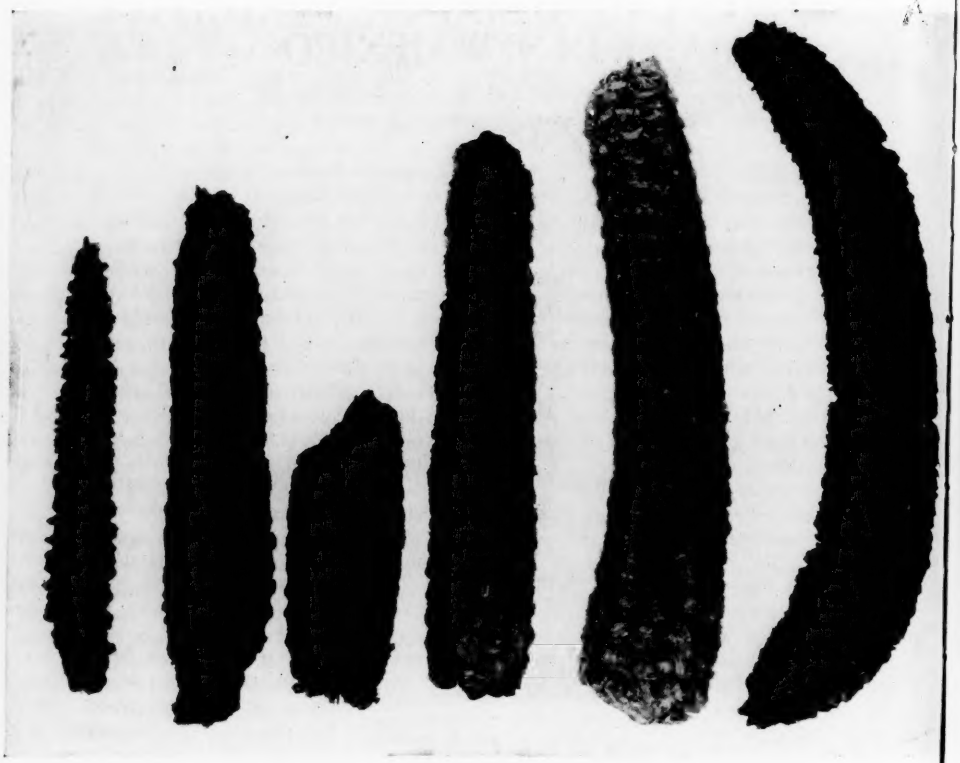
Since the JOURNAL OF HEREDITY has frequently in the past been the medium through which students of maize have announced important new discoveries, it is appropriate that this most recent development toward the solution of the intriguing mystery of the origin of maize be recorded on its pages. We are indebted to Mr. Robert C. Cook, its Editor, for making possible the publication of this summary.

The prehistoric remains to be described in this paper were uncovered from the accumulated refuse of an abandoned cave known as Bat Cave, located in Catron County in New Mexico. This refuse, which was some six feet in depth, is conservatively estimated to represent a period of approximately three thousand years, beginning at about 2500 B.C. and ending at about 500 A.D. to 1000 A.D. This tentative dating is based upon the fact that the refuse rested directly on a layer of sand and dust which was probably formed between 5500 B.C. and 2500 B.C. A gravel layer believed by geologists to have been laid down in an earlier pluvial period underlies the sand and dust. The absolute dating of the remains is not, for our purpose, of overwhelming importance. Much more significant is the relative age of the specimens uncovered in different strata of the refuse.

The refuse was removed in strata, each approximately one foot in thickness, and the specimens from each stratum were studied separately. The remains of maize comprised a total of 766 specimens of shelled cobs, 125 loose kernels, eight specimens of husks, ten of leaf sheaths, and five of tassels and tassel fragments. Most of the specimens, even from the lowest stratum, were extraordinarily well-preserved, even the tiny plant hairs on the epidermis of the glumes and the surface of the cupules being still intact. Indeed, most of the material is in such an excellent state of preservation that the botanists would be inclined to question the geologists' estimate of its antiquity, did not the specimens from the different strata exhibit a distinct evolutionary sequence.

The most important new evidence concerning the origin and evolution of maize is obtained from the cobs. Of the 766 specimens of cobs removed from the refuse, 471 were so well-preserved that their internal characteristics could be easily studied and described. This was

*This expedition was in cooperation with the University of New Mexico, and was financed in part by the Viking Fund of New York City.



THE BAT CAVE SERIES

Figure 7

The largest cobs (two thirds natural size) found in each of the six successive strata in the Bat Cave material. Although there has been a progressive increase in maximum size from stratum to stratum, the type found in the first stratum has persisted throughout the series.

done by snapping the cobs in two and examining the two ends thus exposed under a dissecting microscope. The amount of information that can be gleaned from the broken ends of the corn cobs is truly astonishing. Among the characteristics which we studied were the texture of the rachis, its diameter and its size in relation to the diameter of the entire cob. The lower glumes were classified with respect to their size, texture, hairiness, and venation; and the upper glumes with respect not only to these same characteristics but also to shape. From these intensive studies of the cob, we learned a great deal about the kind of corn which the Bat Cave people grew. We also discovered, as an unwelcome but inevitable by-product of our botanical studies, that corn cobs, centuries ago, were already being put to the use which was immortalized in a rarely-published but widely-circulated poem attributed to James Whitcomb Riley.

Cob Structure

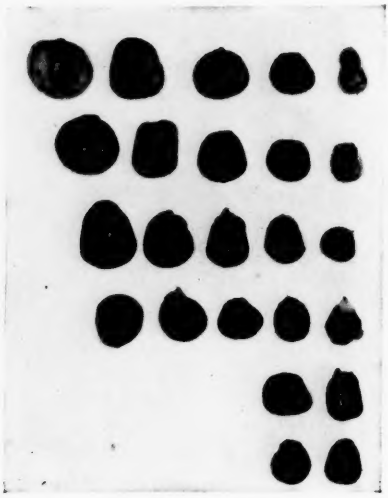
All of the cobs found in the lower strata are small, slender and possess prominent glumes. Twenty percent of them are definitely true pod corn. The glumes which are chaffy, or at the most fleshy, are quite conspicuous in relation

THE "HUSK" INVOLUCRE

Figure 8

A fragment of husk found in Stratum II and the kind of ear which it must once have covered. The husk consists of four leaf sheaths which show no evidence of ever having enclosed an ear. They probably formed an involucre around the base of the ear. (Two-thirds natural size.)

to the diameter of the rachis, and many of the upper glumes are shaped like a boat-end, indicating that they had once enclosed a kernel. The remaining eighty percent of the cobs in the lowest stratum represent a weak form of pod corn. True pod corn and weak pod corn are the only types found in either of the two lower strata. There is not the slightest evidence that the maize at these lower levels has been derived in any way from teosinte. On the contrary, the evidence



KERNEL SIZE
Figure 9

Variation in kernel size in the six successive strata of the Bat Cave material. The kernels, like the cobs, have increased in mean size from stratum to stratum, but the smallest size has persisted throughout the series. (Natural size.)

that it could not have been derived from teosinte is almost overwhelming.

The cobs become progressively larger and thicker from stratum to stratum, as shown in Figure 7, in which the longest cob from each stratum is illustrated. It is important to note, however, that the primitive cobs characteristic of the lower strata do not completely disappear from the scene when larger types make their appearance in the upper strata. The most important change from stratum to stratum has been, not a mere increase in size, but an enormous increase in the total variation. This, we believe, may prove to be one of the most important features of evolution under domestication and it may also have a bearing on the origin of some of the sudden large-scale changes in organisms which sometimes seem, on the basis of the fossil record, to occur in nature.

Teosinte Not an Ancestor

Although there is no evidence of an origin from teosinte in the primitive maize of the lower strata, there is strong evidence of an introgression of teosinte into maize at a later period. This manifests itself in cobs in which both the rachis and the lower glumes are bony, and in which the cupules of the rachis are covered with short prickles rather than with hairs. Several cobs were found with the distichous arrangement characteristic of teosinte and two were encountered which bore single spikelets, also a teosinte characteristic. All of these manifestations of teosinte introgression, however, are conspicuously absent from the lower strata. They make their first appearance in Stratum III and reach their highest frequency in Stratum V, declining for some reason in the uppermost stratum.

The kernels of the Bat Cave maize, like the cobs, show a distinct evolutionary sequence with respect to size, becoming progressively wider from stratum to stratum. The smallest kernels, characteristic of the lowest stratum, are corneous and were undoubtedly capable of popping. Like the primitive cobs, they persist until the end of the series (Figure 9). Thus in kernel width, as in cob size, the most important feature in the evolutionary series is the progressive increase in the range of variation.

Of the eight specimens of husks found in the Bat Cave remains, the single specimen which occurred in Stratum II is by far the most interesting and important. It is more than twice the length of the longest cob found in either of the two lower strata and its stem or shank is so slender that it could only have borne an ear of the type commonly found in these two lower strata. The husk and an ear of this type are illustrated in Figure 8.

Husks Covered Only Base of Ear

The husks, which comprise four glabrous, largely undifferentiated leaf sheaths, show no evidence of having ever been shaped around an ear. Instead, they seem to have functioned as an involucre, surrounding the ear at its base but not enclosing it completely. Although this is not exactly the type of pistillate inflorescence which students of maize

usually visualize when picturing wild corn, there is no reason to suppose that a maize plant of this general type could not have existed in the wild. It is possible, therefore, that the primitive maize found in the lower strata of Bat Cave, although probably not itself wild maize, is not far removed from wild maize in its characteristics.

The husks, like the cobs, in this prehistoric material are quite different from those to be expected in teosinte derivatives and furnish additional direct and convincing evidence that maize did not originate from teosinte.

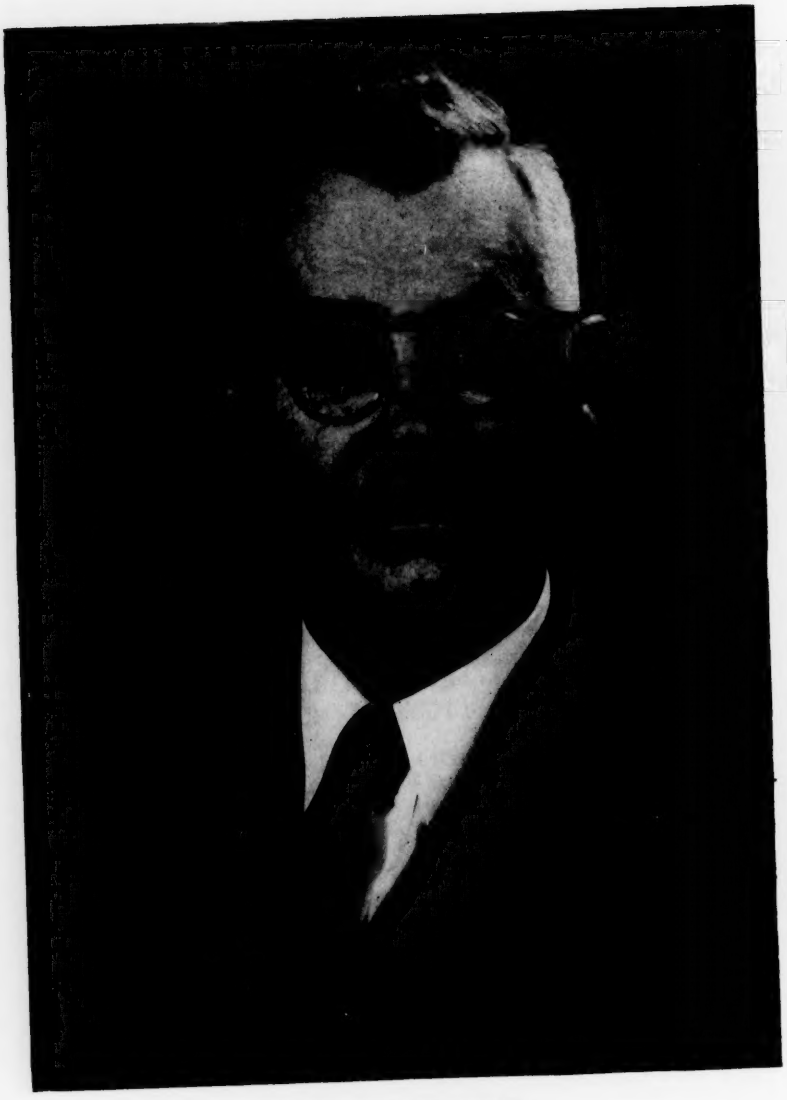
An artist's reconstruction of an ear of primitive Bat Cave maize, executed by Mr. Gordon W. Dillon, is shown in natural size in Figure 6. In its spiral phyllotaxy and the nature of its glumes the reconstruction is based upon an actual specimen found in Stratum I. The size of the kernels enclosed in the glumes is based upon estimates, and, since the prehistoric cob which served as a model was not intact with respect to length, the length of the reconstruction is also based upon an estimate.

A complete description of the specimens found in Bat Cave and an analysis of the evolutionary changes which occurred during a period of not less than three thousand years is being published in the Harvard University Botanical Museum Leaflets. From these studies three definite and well-supported conclusions with respect to the origin of maize may be drawn. 1. Primitive maize was both a pod corn and a pop corn. 2. Maize did not originate from teosinte. 3. Maize has been strongly modified in the later stages of its evolution by an introgression of teosinte (or Tripsacum) germplasm.

The question of where maize originated as a wild plant is not solved by the new evidence.

ONE HUNDREDTH MEETING OF BRITISH GENETICAL SOCIETY

The Genetical Society of Great Britain, founded in 1919 by William Bateson, will hold its 100th Meeting on June 30th and July 1st, 1949, in Cambridge. To mark the occasion guest speakers will review the early days of Genetics, and there will also be comprehensive demonstrations of genetical work now in progress in Great Britain. Genetical Societies abroad have been informed of this meeting, to which all geneticists are cordially invited. Details may be obtained from the Secretaries, G. Pontecorvo, Department of Genetics, The University, Glasgow, W.2., and H. G. Callan, Institute of Animal Genetics, The University, Edinburgh, 9.



ERNEST W. LINDSTROM

1891-1948

ERNEST W. LINDSTROM

1891-1948

GENETICS lost another of its able early leaders when Ernest W. Lindstrom, Professor of Genetics at Iowa State College, died on November 8th after several months of illness. Though born and reared in a city, his love of the open country and his keen interest in plant life blossomed strongly, even at an early age. He intended to become a forester and began his college with three years' study at Colorado College. Intrigued by the then startling developments in genetics, he swung his interests to that exciting field but always continued to appreciate keenly the whole range of problems in botany, including the evolutionary aspects and the possible applications to agriculture.

Finishing his Bachelor's degree at Wisconsin in 1914, he went directly to Nebraska to begin graduate work under the guidance of Dr. R. A. Emerson. He went with Emerson to Cornell that autumn. There he was active in the group of eager and able men whom Emerson trained and inspired to exert such a prominent influence on the development of genetics in the United States since the middle 'teens. The men of this group will always remember Lindstrom's rare combination of enthusiasm, stimulating skepticism, and high good humor. On receiving his Doctor's degree at Cornell in 1917 he went immediately into the Air Force where he was commissioned as a pilot and reached the European scene of action early in the autumn of 1918.

On returning to civil life in 1919 he became right-hand man to the late Dr. L. J. Cole in the Genetics Department at the University of Wisconsin. There he also pursued vigorously his own investigations on the inbreeding of corn. He came to Iowa State College in 1922 to build the Genetics Department which had just been authorized. He chose to develop it as a small department with an able staff, serving the college primarily as a catalytic center where all interested in applying genetics to whatever species could find common and interesting ground for discussing their problems. The department also taught the introductory and the advanced fundamental courses in genetics.

In 1927-28 Dr. Lindstrom was given a leave of absence to act as Assistant Director of the Rockefeller Foundation's International Education Board in Paris. There he had abundant opportunity to inspect, appraise and keep in touch with the work in genetics all over Europe, as well as to integrate this in his own mind with work in the several other fields of science. Few geneticists in America became so well known personally to their professional colleagues in Europe as Dr. Lindstrom did.

In 1944-45 he had another year's leave of absence which was especially welcome then, since he was somewhat weary of his administrative duties as Vice-Dean of the Graduate College. During that year he taught genetics and organized the research program in plant breeding for the agricultural college of the National University of Columbia at Medellin.

He was prominent in cooperative genetic affairs in the United States and took an active part in the Maize Genetics Group. He was successively Secretary, Vice President and President of the Genetics Society of America during the years 1938 to 42. He was also Secretary of the American Society of Naturalists and an officer of other professional groups. He participated actively in the fifth, sixth and seventh International Genetics Congresses.

The many graduate students who came under his influence will never forget his classes and his seminars, more especially his wit and his lively but constructive skepticism. His wholesome scorn of sham and pretense, his acid comments on ambiguities, his thorough respect for facts and his lively efforts to promote clear thinking in his students, even to acting sometimes like a prosecuting attorney trying to entangle them, — all these were to the end of making clearer

the distinction between what the student really knew, what he surmised, and what he had read but didn't understand. This made his seminar one of the most popular on the campus. The leading of it was an experience that his students will never forget.

In accordance with his wishes and as befitted one who loved his work so intensely and disliked ostentation and ceremony, the funeral services for him were kept simple. Instead a Lindstrom Memorial Genetics Library is being established in the library of the Iowa State College. Funds to help with this may be sent to the Genetics Department, Iowa State College.

Professor Lindstrom published some fifty papers. These appeared mostly in scientific journals dealing with genetics, botany or agriculture, although some were in publications of the colleges at which he worked. Most of his papers concerned the genetics of corn or tomatoes and presented directly the observed experimental facts, but the implications for general genetic or evolutionary theory were not neglected. He was a bulwark of sound counsel to many plant breeders associated with the development of hybrid corn, both in the commercial applications and in the strictly research phases. This he did to a larger extent than would be guessed by the number of times his name appears in print.

The going of so able and influential a man many years sooner than might have been expected, causes unusually intense sorrow and regret but his influence will still have its effects in many unexpected places through the way his thinking, his comments and his advice have helped shape the attitudes of his students and colleagues. Genetics is farther along and is already a sounder science than if he had chosen some other field of work.

JAY L. LUSH

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EGYPT'S POPULATION GROWTH

The pressure of Egypt's rapidly growing population on her very exiguous soil has been preoccupying Egyptian economists and sociologists during the last fifteen or twenty years. But the problem is not peculiar to Egypt; it is part of a world-wide phenomenon which can be seen equally well in India or Indonesia today or in Western Europe during the 19th century. Briefly put, the population of these countries is growing, or has grown, because the secular balance between births and deaths has been upset. For in a pre-industrial society the death rate is always high, owing to inadequate nutrition, defective hygiene, the spread of epidemics and the loss in lives resulting from disorders and wars. In order to compensate for this high wastage, the society favours those customs and institutions that promote a high birth rate, such as stigmatizing celibacy, encouraging marriage at an early age, honoring parenthood and so forth. When as a result of the spreading of industrial civilization, order and security prevail, hygienic conditions improve and more food becomes available, the first effect is a decline in the death rate. The birth rate, however, which is determined mainly by social and religious factors, remains for a long time at its previous high level. It is only when an industrial civilization has prevailed sufficiently long to change the whole customs and outlook of the population that birth rates begin to decline, as they have been doing in Western Europe and North America. Egypt is at present in the first stage, the stage of declining death rates unaccompanied by falling birth rates.

Egypt's population in the Pharaonic, Roman, and early Arab times is generally estimated at 6-7 millions. Long centuries of Mameluke misrule, however, combined with the diversion of the trade routes linking Europe with India, caused the population to drop heavily, to perhaps 2,500,000 by the end of the 18th century.

Mohammad Ali Pasha's enlightened and firm rule and the economic expansion that set in under his reign set the population curve on an upward course from which it has not since deviated. . . .

As a result of these factors, the population doubled in half a century, standing at about 6,800,000 at the time of the British occupation in 1882. . . . The reported population of 1947 (19.04 million) is generally believed to be inflated but it is very unlikely that the true figure is lower than 18,000,000 which would give an increase of about 13 per cent over the decade. . . . Two facts should be borne in mind. First, Egypt's population has increased sixfold during the last hundred years, from about 3,000,000 to some 18,000,000, a rate of growth probably unparalleled by any purely agricultural country. Second, Egypt is perhaps the most densely populated country in the world.—CHARLES ISSAWI. *Milbank Mem. Fund Quart.* Vol. 27: No. 1, Jan., 1949.

LOSS OF OIL FROM HEVEA SEED

A Variation having Phyletic and Economic Implications

J. T. BALDWIN, JR.
College of William and Mary, Williamsburg, Virginia

IN December of 1948, after an interval of two years, a dried-plant collection of *Hevea* which I had assembled during 1942-1944 from throughout the Amazon Valley was re-examined. From rapid shuffling of herbarium sheets it was strikingly apparent that some of them were marred by oily splotches. The specimens had been mounted in 1945 on standard herbarium paper, and for many of the collections seed had been obtained and were placed in "pockets" of heavy bond paper affixed to the sheets. All species of the genus, not numbering more than nine,[1,3] were represented, and for some collections of each species seed were available.

It was soon discovered that the fatty disfigurement of the herbarium preparations resulted from seed-loss of oil. So much oil has escaped from the seed of two species that the "pockets," the herbarium sheets, and, in some instances, the manila genus covers have extensive greasy areas. But the seed of other species—except for those from occasional trees to be noted below—have not even spotted the "pockets" which contain them. These observations have phyletic implications and may likewise be of economic importance, for, in a minor way, the oil of *Hevea* seed has been used (See Jamieson[8] for references.).

Relationships Among Species

Hevea rigidifolia has seed exhibiting marked loss of oil. Specimens were collected from only two trees of this species, and they do not match the type.[2] Seed of both collections have been emitting oil in considerable quantity. Schultes[9] questioned the reference of these collections to this species, yet, amusingly enough, he assigned here a seedling from one of the trees in question. The few seedlings grown in 1944 at the Instituto Agronômico do Norte, Belem, Pará, Brazil, had the rigid first true leaves that are peculiar to this species.[2] I saw those plants again in 1947 and was satisfied that they were *H. rigidifolia.* However, I[2] had been in error in doubting the notation on *Froes 21253* that the leaves of this tree are "somewhat pendant"; my Belem seedlings now show that character, as is evident in a photograph of one of them published by Schultes.[9]

That writer,[9] after having spent a part of 1947-1948 in the geographic area of *H. rigidifolia,* claimed no knowledge of the plant in nature, and from limited herbarium material he decided that this species is "exceptionally stable." No species of *Hevea* is stable. They all vary, and largely because of widespread introgressive hybridization.[3,10] That has probably been the most significant factor in the evolution of the genus. So to interpret *Hevea* one must be able to comprehend the fundamental mechanics of gene insertion from one genotype into another.

Since seed of only two trees of *H. rigidifolia* have been available for study, and because those trees are not typical, seed-loss of oil may not prove to be characteristic of the species.

Several lots of seed are at hand for the second species; they have all been discharging oil in conspicuous manner. This species is not so easily designated. Its nomenclatorial history is complex. This tree is often relegated to *H. pauciflora,*[6] and, from the very beginning, it has been confused with *H. brasiliensis* (Willd.) Muell. Arg., a species published and illustrated in 1824. The tree in question was first collected by Humboldt and Bonpland on the Orinoco—

within present limits of Venezuela—and, unfortunately, was described in 1825 as *Siphonia* (a synonym under *Hevea*) *brasiliensis* H.B.K. Huber[7] and Chevalier[5] reviewed this taxonomic problem, and they would refer the Orinoco plant to *H. Kunthiana* (Baill.) Huber. And in the Kew herbarium is informative correspondence of I. H. Burkill with A. Chevalier and N. L. Diels relative to this matter.

Baldwin[3] reported on a tree which the natives of the upper Rio Negro region call *"seringa* (rubbertree) *da serra"* and which he suggested was most likely cospecific with the Orinoco plant just discussed. He designated that tree *H. pauciflora,* but with the proviso that possibly this name should properly be assigned to the entity which he referred to as *H. confusa.* Study in European herbaria during 1948 has convinced me that such is so. Accordingly, *H. Kunthiana* is accepted here for the Orinoco plant, for *"seringa da serra"* of the upper Rio Nigro, and for certain collections from British Guiana and Surinam. The species will be discussed in detail elsewhere.

That seed of both *H. rigidifolia* and *H. Kunthiana* lose oil in significant amount suggests close genetic relationships between these species. Baldwin[2,3] stated that their seed are much alike and that the natives of the upper Rio Negro eat the seed of both species: he found a tree of *H. rigidifolia* that had been cut for its almost-mature seed and recorded that trees of *H. Kunthiana* are not uncommonly planted for their edible seed. Though the natives "designate the latter tree *seringa,* they say it has seed like *cunury."* Baldwin and Schultes[4] discussed the use of seed of *cunury—i.e.,* of *Cunuria,* a genus with affinities to *Hevea*—as food of Amazonian Indians. (Almost a hundred years ago Richard Spruce reported the use of seed of both *Hevea* and *Cunuria* as food in that region.) And Baldwin[2,3] has mentioned the possibility of introgression between these genera. Pertinent here is the fact that *Cunuria* seed among my collections evidence no loss of oil.

Occasional trees of other species than the two already designated have seed from which oil escapes. Most likely those individuals have certain genes derived, by hybridization, either from *H. rigidifolia* or from *H. Kunthiana.* Seed from some representatives of *H. pauciflora* and of *H. nitida* (*H. viridis*) from the upper Rio Negro region, and therefore within the *rigidifolia-Kunthiana* area, have been giving off oil. No collections of these species outside that general area show an oil loss. Baldwin[2,3] considered these four entities to constitute a single complex. Seed of certain collections of *H. Benthamiana** from the upper Rio Negro are likewise losing oil. Ducke[6] and Schultes[9] considered this species to be evolutionarily close to *H. rigidifolia.* Baldwin[3] suggested that the entity here designated *H. Kunthiana* probably contributed to the development of *H. brasiliensis.* Seed from *brasiliensis* trees from near Iquitos, Peru, and from 450 miles up the Rio Juruá in Brazil have been losing oil. Interesting in this regard is a statement by Schultes[9]: "The resemblance of the seed of *Hevea rigidifolia* to that of one form of *H. brasiliensis* of the upper reaches of the Solimoes must be interpreted as coincidental." Seed from a tree of *H. guianensis* var. *lutea* at São Felippe on the Rio Negro are losing oil. Fruit of that individual were curiously "sculptured" and remotely reminded one of the wrinkled dried fruit of *Cunuria crassipes.* Schultes[9] recognized a likeness between the seed of var. *lutea* and that of *H. rigidifolia.*

Economic Implications

What oil-escape from *Hevea* seed means and why the species differ in this regard, one can not at the moment say. But possible economic implications are immense. Do some seed contain much more oil than others? Do enzymes oper-

******Hevea discolor* (Spruce ex Benth.) Muell. Arg. was based on type material now usually referred in part to *H. Spruceana* (Benth.) Muell. Arg. and in part to *H. Benthamiana* Muell. Arg.; since *H. discolor* antedates the last name, *H. Benthamiana* would seem to be invalid.

ate differentially among the species for release of oils? Are some of those oils especially valuable? These and other questions arise. Only by experimentation can they be answered. It is urgently desirable, therefore, that the comparative chemistry of single-tree lots of seed of the various entities of the genus be determined.

References[8] at hand indicate that seed-oil analyses have been made for *H. brasiliensis* alone: "The kernel, which amounts to about 50 per cent of the seed, contains from 42 to 50 per cent of oil, an active lipolytic enzyme, and a cyanogenetic glucoside. The oil is obtained from the seeds of the cultivated trees either by expression or solvent extraction and usually has a very dark red color. The cake or extracted meal is used as a fertilizer or feeding stock. The oil is chiefly used in the manufacture of soap, but it can be used as a paint oil, particularly after it is refined. . . . The oil is said to be a fairly good drying oil and gives a hard, transparent film."

That the Amazonian native seems especially to select for food the seed of *H. rigidifolia* and of *H. Kunthiana* and that oil escapes freely from seed of these species are reasons for according this phase of the genus particular study. Certain individual trees may well supply a basis for a seed-oil industry. Or from such trees genes might be introduced into plantation rubber in order that seed may, as recently suggested by Seibert,[11] be used for by-products. Seed of these two species should be obtained for analysis as soon as possible. In 1944 the mid-season for fruit maturity of *Hevea* on the upper Rio Negro came in March.

The plantation industry faces rising production costs as well as competition from synthetic rubber. Trees with a high level of efficiency are necessary to guarantee survival of an agriculture based mainly on natural rubber. If trees can be made, via seed, to supply food for the workers in addition to an optimum amount of latex, the future of the industry is rather well assured. Thereby, too, nutritional deficiencies for thousands of people throughout the tropics of the world might be lessened, and thousands of acres of land might be saved from ruinous cultivation of non-tree crops.

Hope for the synthesis of rubber- and food-producing trees comes from the known existence (mentioned above) of individuals of *H. brasiliensis,* of *H. Benthamiana,* and of *H. guianensis* var. *lutea* with seed from which oil escapes. These groups include the best producers of rubber; their aberrant representatives might perhaps have seed with pronounced values for oil or food. If so, they indicate the goal toward which a plant-breeding program should be directed.

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✦

EARLY GREEK THEORIES OF SEX DETERMINATION

IN genetics, as in almost every other branch of knowledge, the ancient Greeks had several theories; and here, as elsewhere, some of their hypotheses were closer to the mark than most geneticists today believe. In ancient Greece, as in modern America, there was a tendency to discount scientific genetic specu-

lation in favor of less adequate popular mythology; but the basic conception of a genetic matrix was really evolved by the Hippocratic medical school, in the Fifth Century before the Christian era.

In this Hippocratic tradition[1] the mechanism of sex-determination was described by a kind of combination-diagram. Each parent produces two kinds of "seeds." When two of these seeds meet, their union is thought of as though a struggle took place, and one of them always won out, "dominating" the other, which was weaker. The sex transmitted by this "dominant" seed determines the sex of the offspring.* The nature of the other seed in the compound, which is dominated, determines the degree of masculinity or femininity, so that in fact not just two sexes, but *six* degrees of sexuality are recognized by the theory.

A combination matrix illustrating all possible pairings of seeds contains many impossible combinations. Since one and only one of the seeds must win and dominate, no combination of two dominating or two dominated seeds is possible. Further, the seeds of the two parents differ in strength; a male seed from the male parent will always dominate a male seed from a female parent, and vice-versa. Beginning with a schematism of all theoretically possible combinations, and eliminating those not in accord with this hypothesis of conflict and dominance, leaves just six viable combinations. (See Table I.)

TABLE I. Theoretical combinations of male and female sex-elements.

M represents a male seed which dominates; *m*, a male seed which is dominated; *F*, a female seed which dominates, and *f*, a female seed which is dominated. The first symbol in each combination represents the seed contributed by the female parent, the second symbol (in italics) that contributed by the male. Combinations marked * are impossible, because they violate the postulate that one and only one seed can be dominant. Combinations marked † are impossible, because they violate the postulate that a male-contributed male seed cannot be dominated by a female-contributed male seed, and vice-versa.

		MALE PARENT			
		M	*m*	*F*	*f*
FEMALE PARENT	M	M*M**	M*m*†	M*F**	M*f**
	m	m*M*	m*m**	m*F*	m*f**
	F	F*M**	F*m*	F*F**	F*f*
	f	f*M*	f*m**	f*F*†	f*f**

This elimination leaves the following viable combinations: M*f*, m*M*, f*M*, m*F*, F*m*, and F*f*. The resulting six sex-gradations are described as follows: m*M*—super-male, supremely masculine; M*f*—normal male; f*M*—subnormal masculine, effeminate male; F*f*—super-female, supremely feminine; m*F*—normal female; F*m*—subnormal female, masculine or mannish woman. Of these, the super-male was considered a typical homosexual, the subnormal, mannish female a typical Lesbian. In popular Greek belief, homosexuality in men was associated with excessive virility, and heterosexuality with greater effeminacy.

Prof. R. G. Bury, in *The Symposium of Plato*[2] discusses Aristophanes' satiric speech in the *Symposium*[3] as a burlesque of the Hippocratic theory just presented, above. But in this satirical version, only three sexes are recognized. Aristophanes tells how Zeus punished the original men, who had "four legs, four arms, two faces and two sets of sex-organs" by bisecting them. The resulting halves, each seeking its original complement, formed the three classes (1) halves of double males, (2) halves of double females, (3) halves of heterosexual originals. Of these, (1) corresponds to the Hippocratic m*M*, (2) to the F*f*, and (3) to the other combinations indifferently; since Aristophanes' interest is centered in "explaining" homosexual and heterosexual behavior.

Like many inventors of contemporary folklore concerning heredity, Plato's comic poet is depicted substituting a buffoonish mythology for the more technical matrix explanations in terms of "seeds" favored by his contemporaries in the scientific and medical professions.

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*The terms "seed" and "dominant" are intended throughout in their Hippocratic not their modern technical sense; thus a "seed" is the postulated something that each parent contributes, and of these two "seeds" one is assumed always to be stronger, hence to "dominate" the other.

SYSTEMATIC PROCEDURES FOR CALCULATING INBREEDING COEFFICIENTS

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THE coefficient of inbreeding devised by Wright[2,3] has proven most useful in following the progress in the development of inbred lines of sheep. No regular system of inbreeding is possible with sheep as there is considerable overlapping of generations, particularly of females in the flock at any one time. Furthermore, the length of generation for males is usually less than for females and the breeding of males within female generations is never at random. These conditions may apply to other farm animals, particularly cattle.

When inbreeding is to be extended for many generations, as in the development of inbred lines of sheep, the calculation of inbreeding coefficients by ordinary pedigree analysis becomes increasingly complex in succeeding generations as shown by Lush.[1] A measure of inbreeding is still essential because the degree of inbreeding varies widely within lines and also affects production traits.

The formula for the inbreeding coefficient originally devised by Wright[2,3] and modified by Lush[1] is:

(1) $F_X = \frac{1}{2} \Sigma[(\frac{1}{2})^n(1+F_A)]$

where F_X is the inbreeding coefficient of the individual X; n is the number of generations between individuals in a line by which the parents are related; and F_A is the inbreeding coefficient of the common ancestor A, from whom the lines of descent arise. All such lines of relationship are evaluated separately and added together.

The relationship of the parents (S and D), for the purpose of calculating the inbreeding coefficient of the offspring, would be

(2) $R_{SD} = \Sigma[(\frac{1}{2})^n(1+F_A)]$

which is the genetic covariance, but will be called the numerator relationship since it is the numerator of the true relationship

(3) $R = \dfrac{\Sigma[(\frac{1}{2})^n(1+F_A)]}{\sqrt{(1+F_S)(1+F_D)}}$

as given in Lush.[1] The numerator relationship for any pair of parents is twice the value of the inbreeding coefficient of the offspring.

From (1) and (2) the numerator relationship of parent (S) to offspring (X) becomes:

(4) $R_{SX} = F_X + \frac{1}{2}(1+F_S)$

and the numerator relationship of an animal (X) to itself is $1+F_X$.

The calculation of inbreeding coefficients may be simplified by using methods of combining these numerator relationships to avoid tracing out each line of descent on each pedigree. One method involves the determination of the numerator relationship of a sire to each of his ancestors through which he may be related to any dam. These numerator relationships are arranged in a table with the appropriate derivatives in columns designating the number of generations that the common ancestor may be removed from the dam. These derivatives are then added for each ancestor in the dam's pedigree and the result divided by 2 to give the inbreeding coefficient of the offspring.

The numerator relationships of a sire to his ancestors will be calculated from the pedigree of 1646RW presented in Figure 11. Only essential ancestors have been included and some relationships among foundation animals have been omitted for simplicity of presentation. Beginning with the sire the n values for number of generations to each ancestor are recorded just above that ancestor's number. The parents are 1; simple grandparents are 2 and great-grandpar-

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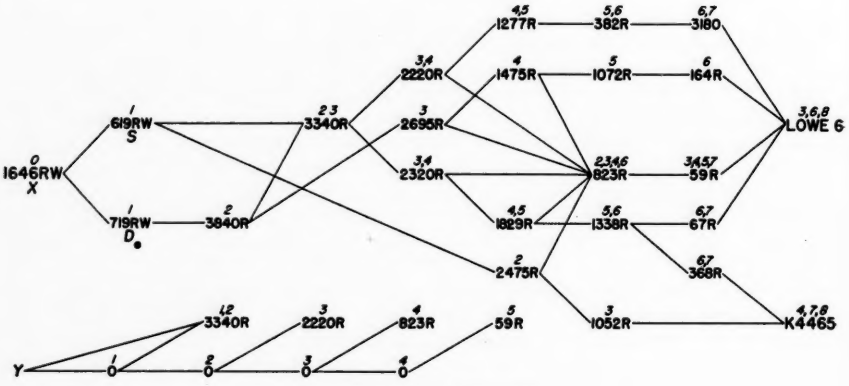

PEDIGREE OF 1646RW

Figure 11

As a guide to computation of inbreeding coefficients this skeleton pedigree is presented. The *n*-values are given just above the pedigree numbers. The pedigree of ewe *Y* is discussed on page 53.

ents are 3, etc. The ram 3340R is a grandparent on one side and a great-grandparent on the other or 2, 3. These values of *n* may be combined because they are exponents of ½. Thus $(.5)^2 + (.5)^2 = (.5)^1$ and $(.5)^3 + (.5)^3 = (.5)^2$. The *n* values for Lowe 6 are 3, 6, 8. The contributory values are 7, 8 through 3180; 4,5,6,8 through 59R; 7,8 through 67R; and 7 through 164R. Combining exponents 4,5,6,7,7,7,8,8,8 becomes 3,6,8. The numerator relationship of any ancestor having only direct relationship to the final descendant will be the numerical transformation of the *n* values for that ancestor. Thus the numerator relationship of 1646RW to Lowe 6 is $(.5)^3 + (.5)^6 + (.5)^8 = .125 + .01562 + .00391 = .14453$.

The individuals in the pedigree of 1646RW are then listed as shown in Table I, with columns for the inbreeding coefficient of the individual, the numerator relationship to 1646RW and *n* derivatives of the numerator relationship where $R_{XA}(.5)^n$ are the derivatives. If a calculator is not available, it may be convenient to express the numerator relationship by the combined exponents of (.5) and proper derivatives will be obtained by adding the appropriate number of generations from the dam's pedigree to each exponent. All of the exponents from a dam's pedigree are then combined before converting to the numerical equivalent. The numerator relationships are calculated progressively down the table from parents to offspring.

The procedure of calculating the numerator relationships of two animals in the pedigree will be given in detail. First, 59R has one listed parent. The direct paths of *n* are 3,4,5,7 for 59R as shown on the pedigree. In addition there is indirect relationship through Lowe 6. The paths for this would be 4,7,9 or half the relation of Lowe 6 to 1646RW (3,6,8) if none of the paths were through 59R. The amount which comes through 59R is 3,4,5,7, the direct paths to 59R, plus the path from 59R to Lowe 6 and back to 59R, or 5,6,7,9. The complete operation involves adding the numerical values for the paths, 3,4,5,7,4,7,9 and subtracting those for 5, 6, 7, 9 giving the numerical relationship of 59R to 1646-RW of .24219. Various shortcuts may be used in obtaining this value. For instance, the direct relationship of 59R plus half the relation for Lowe 6 minus one-fourth the direct relation for 59R equals .24219. In many cases the path

values can be combined mentally.

Indirect relationships, when parents are inbred, necessitate more complex calculations. In the relationship of 3340R to 1646RW, the direct paths are 2,3. Half the numerator relation for each parent is then added (.18970 for 2220R and .24267 for 2320R, from Table I, $n = 1$). The correction for each parent becomes $(.5)^{n+2}(1+F_A)$ because each parent is inbred. The correction becomes $[(.5)^4+(.5)^5][1+.01562] + [(.5)^4+(.5)^5][1+.26562] = .21387$. The numerator relationship of 3340R to 1646-RW is then .25 + .125 + .18970 + .24267 − .21387, or .59350.

The full equation for the numerator relation of an offspring, O, to the final descendant, X, with indirect relationship through inbred parents (P and Q) of O where n is the direct path values from O to X, may be written:

(5) $R_{XO} = \Sigma(.5)^n + .5(R_{XP}+R_{XQ}) - \Sigma[(.5)^{n+2}][(1+F_P)+(1+F_Q)]$

Finally, the numerator relationships of 619RW, the sire, and 719RW, the dam, to 1646RW are used to obtain the inbreeding coefficient of 1646RW, F_X. Equation (4) may be rearranged to

(6) $F_X = R_{XS} - .5(1+F_S)$ or $R_{XD} - .5(1+F_D)$

Substituting, $F_X = .73231 - .58204 = .15027$ or $.65028 - .50000 = .15028$. The two values agree almost perfectly, thus verifying the correctness of all previous calculations. All values have been carried to the fifth decimal place to demonstrate the accuracy of the check. The inbreeding coefficients obtained need not be carried beyond 2 or 3 places for ordinary purposes.

The numerator relationships in Table I for each possible common ancestor are extended for possible values of n in the dam's pedigree by halving each previous figure. Ewe (Y) mated to 1646RW has a pedigree as shown in Figure 11 and a theoretical offspring, Z, will have the inbreeding coefficient

(7) $F_Z = .5\Sigma(R_{XA})(.5)^n$

the values $(R_{XA})(.5)^n$ being found in the appropriate column of n for the particular ancestor. Thus .2968 + .1484 + .0474 + .0288 + .0076 = .5290 which divided by 2 = .2645 = F_Z.

Another method of simplifying the calculation of inbreeding coefficients involves the preparation of numerator relationship charts for all of the animals in an inbred line. This method has been used by Dr. J. L. Lush and associates for many years, but may not be readily apparent to one who is not thoroughly familiar with the calculation of inbreeding coefficients.

The charts may be initiated by calculating the numerator relationships of the foundation animals of the inbred line, or group to be studied, to each other by ordinary pedigree analysis. The sire-ancestor method just described is useful for this purpose. Then numerator relationships of descendants may be computed by use of the formula

(8) $R_{XY} = .5(R_{SY}+R_{DY})$.

The number of numerator relationships to be calculated can be held to a minimum by obtaining only the relationship of each generation group with the preceding and succeeding generation groups. This plan cannot be followed exactly as the generations are irregular.

A form (U.S.D.A.-A.H. Form 405) having 48 columns and 60 lines has been found to be very convenient for constructing these charts for inbred lines of about 30 ewes. The sheep numbers are listed in chronological order down the left hand margin. Numbers of sire and dam and the inbreeding coefficient of the individual are recorded in the first 3 columns. Then the numbers of the first 30 sheep are listed at the top of the next 30 columns. The value of 1 plus the inbreeding coefficient of the individual or its relationship to itself is recorded in the space where the line and column for that individual intersect. The numerator relationships of the first 30 animals to one another are recorded on the lower right portion, and the upper left portion of the top half of the sheet is left blank. The relationships of the second group of 30 animals to those of the first 30 are recorded on the lower half of the sheet. The numbers of this second group are repeated on the top half of the second sheet where their relationships to each other are recorded.

Then the third group of 30 sheep are added on the lower half of this sheet, etc. With larger numbers within generations it is necessary to obtain the numerator relationships of group 1 with 3 and groups 1 and 2 with 4 and 5, etc., depending on the numbers involved.

Some numerator relationships of selected sheep from Figure 11 are shown in Table II to illustrate the procedure followed. It can be seen that the relationship of 3340R to 2475R is found from $.5(.2578 + .3984) = .3281$ and that the inbreeding coefficient of 619RW $= .5(.3281) = .1640$.

Some precautions are necessary in developing the charts. The numerator relationships which are used to obtain the relationship of one animal to another should always be the relationship of the sire and dam of the younger animal to the older animal. This is essential if the two animals are in direct line of descent.

TABLE I.—1646RW pedigree relationships.

	F	R	Values of n				
			1	2	3	4	5
Lowe 6	0	.14453	.07226	.0361	.0181	.0090	.0045
K4456	0	.07422	.03711	.0186	.0093	.0046	.0023
3180	0	.08984	.04492	.0225	.0112	.0056	.0028
59R	0	.24219	.12110	.0606	.0303	.0151	.0076
67R	0	.08984	.04492	.0225	.0112	.0056	.0028
164R	0	.08397	.04198	.0210	.0105	.0052	.0026
382R	0	.08007	.04004	.0200	.0100	.0050	.0025
368R	0	.05468	.02734	.0137	.0068	.0034	.0017
1277R	0	.11036	.05518	.0276	.0138	.0069	.0034
823R	0	.46094	.23047	.1152	.0576	.0288	.0144
1338R	0	.09569	.04784	.0239	.0120	.0060	.0030
1052R	0	.13086	.06543	.0327	.0164	.0082	.0041
1072R	0	.06542	.03271	.0164	.0082	.0041	.0020
1829R	.03125	.32518	.16259	.0813	.0406	.0203	.0102
1475R	.03125	.29443	.14722	.0736	.0368	.0184	.0092
2220R	.01562	.37940	.18970	.0948	.0474	.0237	.0118
2320R	.26562	.48534	.24267	.1213	.0607	.0304	.0152
2695R	.26562	.43921	.21960	.1098	.0549	.0274	.0137
3340R	.19922	.59351	.29676	.1484	.0742	.0371	.0186
2475R	0	.42090	.21045	.1052	.0526	.0263	.0132
619RW	.16407	.73231	.36616	.1831	.0915	.0458	.0229
3840R	.24707	.61231	.30616	.1531	.0765	.0383	.0191
719RW	0	.65028	.32514	.1626	.0813	.0406	.0203
1646RW	.15027						

For instance*:

$$R_{619RW\text{-}719RW} = .5(R_{438WP\text{-}619RW} + R_{3840R\text{-}619RW}) = .5(0 + .6010) = .3005$$

and

$$R_{619RW\text{-}719RW} = .5(R_{3340R\text{-}719RW} + R_{2475R\text{-}719RW}) = .5(.4233 + .1777) = .3005$$

but

$$R_{619RW\text{-}3340R} = .5(R_{3340R\text{-}3340R} + R_{2475R\text{-}3340R}) = .5(1.1992 + .3281) = .7636$$

which is correct, while

$$R_{619RW\text{-}3340R} = .5(R_{2220R\text{-}619RW} + R_{2320R\text{-}619RW}) = .5(.4824 + .6152) = .5488$$

which is incorrect.

Any errors made in recording the numbers of the sire and dam or in calculating or recording the inbreeding or relationship coefficients are not apt to be detected in later work and will be carried on indefinitely. It is important therefore that all work be independently checked.

When inbred lines are first started the calculation of inbreeding coefficients by pedigree inspection or by the sire-ancestor method may be more rapid than the development of numerator relationship charts. However, after 5 to 10 generations of inbreeding this will not be true. The clerical work necessary to develop the charts is simple and routine and does not increase with succeeding generations. The use of the charts would permit a rapid appraisal of the degrees of inbreeding of offspring from each of several available sires to be mated with any group of dams within the line, and would make it easy to compute the average inbreeding or *inter se* relationship in the line at any time.

The sire-ancestor method of calculating inbreeding coefficients is most useful when the number of sires is small and the number of females large. It may

TABLE II.—A numerator relationship chart for some sheep included in Figure 11.

No.	Sire	Dam	Inbr. coef.	823R	1475R	1829R	2220R	2320R	2475R	2695R	3340R	3840R	619RW	619RW	1646RW
823R	59R	218R	0	1.0000											
1475R	823R	1072R	.0312	.5312	1.0312										
1829R	823R	1338R	.0312	.5312	.2968	1.0312									
2220R	823R	1277R	.0156	.5156	.2812	.2812	1.0156								
2320R	823R	1829R	.2656	.7656	.4140	.7812	.3984	1.2656							
2475R	823R	1052R	0	.5000	.2656	.2968	.2578	.3984	1.0000						
2695R	823R	1475R	.2656	.7656	.7812	.4140	.3984	.5898	.3828	1.2656					
3340R	2220R	2320R	.1992	.6406	.3476	.5312	.7070	.8320	.3281	.4941	1.1992				
3840R	3340R	2695R	.2470	.7031	.5644	.4726	.5527	.7109	.3554	.8798	.8466	1.2470			
619RW	3340R	2475R	.1640	.5703	.3066	.4140	.4824	.6152	.6640	.4384	.7636	.6010	1.1640		
719RW	438WP	3840R	0	.3516	.2822	.2363	.2764	.3554	.1777	.4399	.4233	.6235	.3005	1.0000	
1646RW	619RW	719RW	.1502	.4610	.2944	.3252	.3794	.4853	.4208	.4392	.5934	.6122	.7322	.6502	1.1502

* A hyphen is used in place of "to" in the subscripts of these formulae.

be used for breeding plans that attempt to avoid inbreeding to determine if that requirement has been met. To aid in preventing inbreeding, sire-ancestor charts for each of several available sires may be developed and the average inbreeding determined for theoretical offspring of each sire if mated to a random sample of ewes. Inbreeding coefficients of offspring resulting from crossing related inbred lines may be calculated to advantage by this method. It may also be helpful in determining the degree of inbreeding in a herd or flock at certain intervals of time where it is not practical to calculate coefficients continuously.

The development of numerator relationship charts is most useful to follow the inbreeding in inbred lines when relatively small numbers of females are involved within a line and when inbreeding is to be continued for many generations. These charts are also more efficient when an inbreeding coefficient is needed for each offspring from the line.

Inbreeding, combined with improved methods of selection, is proving to be a useful method of improving production traits and scientifically increasing the economic value of a breed. Systematic methods of calculating coefficients of inbreeding will increase the scope and efficiency of their use.

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NOT THE PHILADELPHIA DISEASE!

IN a recent note in the JOURNAL OF HEREDITY Professor F. B. Hutt[7] protested against the suggestion of calling hemophilia "the royal disease" and suggested a number of alternative labels which are more appropriate but which, he implied, are not at all necessary. The writer does not wish to criticize adversely Professor Hutt's note as a whole but he does take exception to the following sentence:

> Hemophilia might more appropriately be labeled as Philadelphia disease because it was there first described as a specific clinical entity, or perhaps because of the Quaker lady who bequeathed it to the seven generations of descendants in the pedigree compiled by Davidson and McQuarrie.

Professor Hutt does not give the date of Philadelphia's first acquaintance with hemophilia but I believe it can be shown that no matter what aspect of the disease we take as a starting point, Philadelphia can not claim priority. Even if the Quaker lady (whose name was Jasper) really lived in Philadelphia, she was not the earliest female to be recorded as heterozygous for hemophilia. According to the pedigree,[2] she was married to Sir William Crispin in 1746. Her hemophiliac son, if he was legitimate, must have been born after this date. Hay[5] traced back a pedigree of a hemophiliac family which started in Ipswich, Mass. in 1713, thirty-three years before Miss Jasper's marriage.

It is also highly improbable that hemophilia was described first as a "specific clinical entity" at Philadelphia. Davidson and McQuarrie[2] use the phrase "distinct clinical entity" and state that hemophilia was thus recognized at a very early date, citing the fact that it must have been prevalent in certain Jewish families because of statements in the Talmud concerning circumcision. Nor was the peculiar type of hemophilia's inheritance first recognized in Philadelphia in spite of the fact that both Professor Hugo Iltis[8] who is cited by Professor Hutt in his note, and Professor R. Ruggles Gates[4] give priority to Dr. John C. Otto,[10] a Philadelphia physician. Davidson and McQuarrie[2] also cited Otto's paper.

The writer recently[11] cited an earlier record of the sex-linked inheritance of

hemophilia but did so in a publication which apparently reached few geneticists. In brief, it can be stated that our knowledge of the earlier descriptions of hemophilia is very incomplete but there are scattered records. Abu-l-Qasim (d. 1106) has been credited with describing the disease. Hochstetter[6] did describe it but the writer found no record of its mode of inheritance in his work. Fordyce[3] noted an instance of hereditary nosebleed, the debility passing from father to daughter, but this defect is not sex-linked. However, ten years before Otto's paper appeared, a very clear description of the sex-linked inheritance of hemophilia was published in Chemnitz, Germany. The following is a translation of a passage in the *Medicinische Ephemeriden* of 1793. From pp. 267-268.

And now for a remarkable story. On the fourth of November I was called into the country to an eleven-year-old boy who two days previously had cut himself lightly on the thumb, and who bled to death in spite of all possible means which had been used to stem the flow of blood. A brother of this boy had many years earlier bled to death from a slight wound, and many brothers of his mother had died in the same way. All the feminine members of this family are, as far as I know, free from this sad idiosyncracy. The sister and children of the mother as well as the mother herself have fine white skin, somewhat prominent capillaries and raven-black hair. The women menstruate normally and are completely sound. The men are inclined to nose-bleeding which is somewhat excessive and always frightens them with the horror of death. Indeed this is a case of remarkable interest for physiology and pathology which I myself cannot clearly explain.

Perhaps, so as not to slight our Philadelphia physician, we should include the following excerpt from his paper. Concerning hemophilia Otto stated:

It is a surprising circumstance that the males only are subject to this strange affection, and that all of them are not liable to it. Some persons, who are curious, suppose that they can distinguish the bleeders (for that is the name given to them) even in infancy; but as yet the characteristic marks are not ascertained sufficiently definite. Although the females are exempt they are still capable of transmitting it to their male children, as is evidenced by its introduction and other instances, an account of which I have received from the Hon. Judge Livermore who was polite enough to communicate to me many particulars upon this subject. This fact is confirmed by Messrs. Rogers and Porter, gentlemen of character residing in the neighborhood, to whom I am indebted for some information upon this curious disposition. When the cases shall become more numerous it may perhaps be found that the female sex is not entirely exempt, but as far as my knowledge extends there has not been an instance of their being attacked.

The next year Coxe,[1] writing about a Maryland family, stated that all the sons of Mr. Benjamin Binny died of the hemorrhage but none of his daughters, and shortly thereafter, by 1820, the peculiar type of inheritance of hemophilia was well known.

Thus it appears that in spite of Dr. Otto's paper of 1803, Philadelphia can claim no priority in the recognition of hemophilia either as a disease or as a genetic problem. So there seems to be no reason why the name of Philadelphia should be attached to this debility. The writer suggests, however, that there is no reason either for calling hemophilia "the royal disease." Perhaps as the peculiar inheritance of hemophilia was first described in Chemnitz it could be known as "die Chemnitzische tödliche Blutung."

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